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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
J. M. Steinke
A. P. Shepherd

Serial No.: 07/953,680

Filed: September 29, 1992

For: METHOD AND APPARATUS FOR DIRECT SPECTROPHOTOMETRIC MEASUREMENTS IN UNALTERED WHOLE BLOOD

Group Art Unit: 2505

Examiner: K. Hantis

Atty. Dkt. No.: UTSK:142/BAH

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APPEAL BRIEF

CERTIFICATE OF MAILING
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Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Notice of Appeal dated April 25, 1996. The fee for filing this Appeal Brief is $150.00 and is attached hereto.

A request for a four-month extension of time to respond is included herewith along with the required fee. This four-month extension will bring the due date to October 25, 1996, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Arnold, White & Durkee Deposit Account No. 01-2508/UTSK:142/BAH.

I. REAL PARTY IN INTEREST

The real party in interest is the Board of Reagents, The University of Texas System.

II. RELATED APPEALS AND INTERFERENCES

This application is a continuation-in-part of Application Serial No. 07/313,911, which was the subject of Appeal No. 92-0991, decided July 30, 1992. In that Appeal, the Board affirmed the rejections then applied by the Examiner. The present appeal involves a substantially different specification with substantially different claims, as discussed more fully below. There are no related Interferences.

III. STATUS OF CLAIMS

Claims 1-44 are pending in this application and are presented for appeal.

IV. STATUS OF AMENDMENTS

No amendments after final rejection have been filed.

V. SUMMARY OF THE INVENTION

The present invention is a blood diagnostic method and apparatus unlike any in the prior art. The present invention uses the optical transmittance of unaltered whole blood to achieve an accurate measurement of total hemoglobin concentration and the concentrations of individual hemoglobin species in a blood sample that may include many species of hemoglobin (for example, oxy-, deoxy, carboxy-, met-, and sulfhemoglobin) as well as bilirubin. As defined in the specification, the term "unaltered whole blood" means "whole blood that has been neither hemolyzed nor diluted." [Page 13, lines 18-19.]

Insofar as Appellants are aware, the present invention is the first, and to date only, method and apparatus that permits these measurements to be made -- accurately -- in unaltered whole blood. As a result, the commercial embodiment of the present invention has been enormously successful, and today is the only commercial diagnostic device that is capable of making those accurate measurements in whole blood. Indeed, as set out in the numerous declarations filed in this case and discussed below, the present invention has been characterized as "astonishing" and "surprising," by experts in the field. Two of the principal and leading companies in the field, Instrumentation Laboratory Company and Ciba Corning Diagnostics, after years of trying, abandoned their efforts to measure multiple hemoglobin species in unaltered whole blood, and Instrumentation Laboratory in fact has licensed the present invention.

Some of the advantages realized by the present invention, with its ability to make these accurate measurements in whole blood, are: (1) lower manufacturing costs, (2) simplified mechanical and fluidic components, (3) simplified calibration of total hemoglobin measurement, (4) faster analysis, and (5) greater ease of integration with blood gas analysis systems.

Unaltered whole blood has several different properties that each contribute to intense light scattering and have precluded the measurements now made possible by the present invention. These different properties include "1) the different plasma protein concentrations that determine the refractive index of plasma in one sample versus another, 2) the aggregation of red cells in the sample, 3) the different hemoglobin concentrations inside the red blood cells that alter their refractive index, and 4) the size and shape of the red blood cells, 5) chylomicrons or other light-scattering lipid particles, 6) cell fragments, 7) microscopic clots, and 8) light-sieving effects of sedimented RBCs." [Page 7, lines 25-32.]

In striking contrast to prior approaches, the present invention does not hemolyze or dilute the blood sample before optical measurements are taken, thus completely eliminating the need for mechanical or chemical hemolyzers, and eliminating the need for diluent containers and extensive pumps, plumbing and associated control circuitry. In addition, the blood sample (with red blood cells intact) is preserved for further subsequent analysis. [Page 8, line 27 to page 9, line 2.]

The calculation of accurate concentrations of hemoglobin species corrected for the effects of scattering is accomplished by the present invention by making appropriate measurements of the light scattering by red blood cells and other factors that contribute to light loss in unaltered whole blood, and by using these measurements to correct mathematically the measurements of total

hemoglobin concentration and the concentrations of the individual hemoglobin species. [Page 8, lines 21-27.]

The method of the present invention is practiced using the apparatus illustrated schematically in Figure 6 (a copy of which appears below).

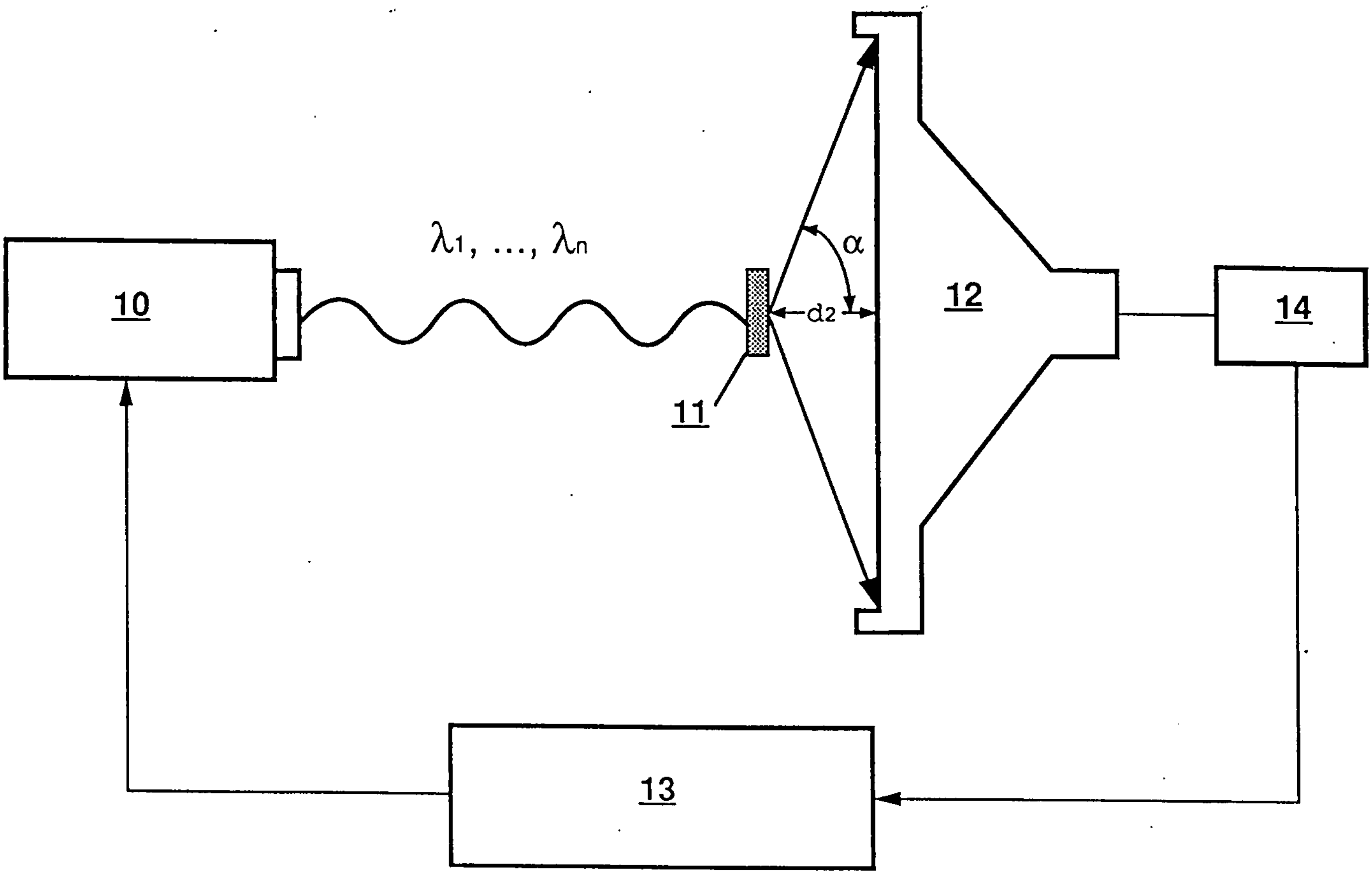

Figure 6.

The apparatus includes a programmed computer 13, a computer-controlled light source 10 that emits a plurality of substantially monochromatic wavelengths, an ultra-thin cuvette 11, a large area light detector 12 and an amplifier 14. [Page 13, lines 23-29.] Computer 13 controls the apparatus to perform the desired measurements and calculates the concentrations of the hemoglobin species contained in a sample of unaltered whole blood under test, corrected for the effects of light scattering by red blood cells, corrected for effects of nonspecific light scattering losses, and corrected for the effects of the finite spectral bandwidth of the plurality of substantially monochromatic wavelengths. [Page 16, lines 3-10.]

Appellants discovered that the intense light scattering caused by undiluted whole blood, which precluded prior art attempts at accurate measurement, could be minimized by carefully selected and designed components. As a result, the various components of the apparatus of Figure 6 are designed to minimize the effects of light scattering relative to absorbance. [Page 15, lines 28-33.] In particular, the cuvette is specially designed to provide a short optical path [page 14, line 33 to page 15, line 3], the distance between cuvette 11 and detector 12 is designed to be small [page 15, lines 5-10], and the detector 12 is designed to have a large area [page 15, lines 12-13].

In addition to the mechanical aspects of the present invention, the present invention applies corrections to the calculated concentrations of hemoglobin species by using additional wavelengths of light and a system of simultaneous equations to correct for deleterious scattering factors. In general:

> n measuring wavelengths are employed to measure k constituent components, with n > k, thereby creating an overdetermined system of equations with respect to the chemical compounds being measured. The n - k extra equations provide a means by which errors due to n - k scattering factors can be compensated.

[Page 20, lines 24-29.] In other words, there are n wavelengths generated, with k of the n wavelengths forming an absorbance subset of wavelengths that have been chosen to measure the k constituent components of the unaltered whole blood sample under study, and with the remaining n - k wavelengths forming a scattering subset of wavelengths that have been chosen to compensate for the n - k scattering factors in the blood sample. The optical densities measured by the apparatus of Figure 6 at each of the n wavelengths are used in a system of n simultaneous equations (similar to the general equation (4) on page 22), along with the extinction coefficients of the components being measured (also see Figure 1) to solve for the concentrations of the components, corrected for the effects of scattering.

Three exemplary embodiments (A, B and C) of the invention are disclosed. In embodiment A, seven wavelengths are used to measure six blood components, while correcting for one scattering factor (red blood cells). [Page 23, lines 18-22.] In embodiment B, seven wavelengths are also used, but only five components are measured while two scattering factors are corrected for (red blood cells and nonspecific light scattering). [Page 22, lines 22-26.] In embodiment C, eight wavelengths are used to measure six blood components, while correcting for light scattering by both red blood cells and nonspecific light scattering. [Page 35, lines 2-7.] Thus, using the words of claim 1 as originally filed, in embodiment A, of the seven wavelengths, six form an absorbance subset of wavelengths leaving one in a scattering subset of wavelengths. In embodiment B, of the seven wavelengths, five wavelengths form an absorbance subset with two wavelengths forming a scattering subset. Finally, in embodiment C, of the eight wavelengths, six form an absorbance subset and two form a scattering subset. Applying the general statement of the invention quoted above from from page 20, lines 24-29, in embodiment

A, n is seven and k is six, in embodiment B, n is seven and k is five, and in embodiment C, n is eight and k is six.

The present invention also includes the correction of the calculation of components of unaltered whole blood for the effect of finite spectral bandwidth of the light sources. [Page 30, line 14 to page 32, line 23.]

The claims of the present application are drawn to a method of determining the concentrations of a plurality of constituent components of unaltered whole blood of unknown composition. With reference to claim 1, a plurality of substantially monochromatic radiation wavelengths is generated, each wavelength of an absorbance subset of the plurality of wavelengths having been selected by its ability to distinguish the constituent components and having been selected to minimize the effects of radiation scattering and to maximize radiation absorbance by the constituent components, and each wavelength of a scattering subset of the plurality of wavelengths having been selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance by unaltered whole blood. Then, a sample of unaltered whole blood of unknown composition is irradiated with the plurality of radiation wavelengths, through a depth of the sample chosen to minimize radiation scattering by unaltered whole blood. Next, intensities of the radiation wavelengths, after passing through the depth of the sample, are detected at a distance from the sample, and over a detecting area, both chosen to minimize the effects of radiation scattering by unaltered whole blood on the determination of concentrations of the constituent components. Finally, the concentrations of the plurality of constituent components of the sample of unaltered whole blood corrected for the effects of radiation scattering are calculated, based upon detected intensities of each of the plurality of radiation

wavelengths, and based upon predetermined molar extinction coefficients for each of the constituent components at each of the plurality of radiation wavelengths. (Claim 1)

The depth of the sample may be in the range of 80 to 150 micrometers (claim 2), preferably approximately 90 micrometers (claim 3). The detecting area is at least approximately 150 square millimeters (claim 4), preferably approximately 600 square millimeters (claim 5). The distance from the sample is within the range of 0 to 10 millimeters (claim 6), preferably approximately 1 millimeter (claim 7). The detecting step may be performed over a cone of radiation emanating from the sample with a half-angle of at least approximately 30 degrees (claim 8), and preferably at least approximately 70 degrees (claim 9).

Another feature of the claimed invention is the correction of the calculated concentrations of the constituent components for the effects of finite spectral bandwidth of the substantially monochromatic wavelengths on the extinction coefficients of each constituent component (claims 10 and 41).

In accordance with one embodiment of the invention, the plurality of constituent components includes oxyhemoglobin (HbO_2), carboxyhemoglobin (HbCO), methemoglobin (Hi), and deoxyhemoglobin (Hb), the method further comprises, selecting the four radiation wavelengths of the absorbance subset by computing an error index for each of HbO_2, HbCO and Hi as the sum of the absolute values of the errors that are induced in the measurement of relative concentrations of HbO_2, HbCO and Hi due to a change in optical density measurements; and selecting a quadruple of radiation wavelengths having minimum error indices (claims 11 and 42). Each wavelength in the quadruple of radiation wavelengths may be within the range of 510 to 630 nanometers (claim 12).

Exemplary quadruples include: 522, 562, 584 and 600 nanometers (claim 13); 518, 562, 580 and 590 nanometers (claim 14); and 520.1, 562.4, 585.2 and 597.5 nanometers (claim 15).

In accordance with another embodiment of the invention, the constituent components may include bilirubin (claim 16). Then, the method further comprises selecting a radiation wavelength within the range of 475 to 500 nanometers for inclusion in the absorbance subset as the radiation wavelength for the measurement of bilirubin, and preferably 488.4 nanometers (claim 17).

In accordance with yet another embodiment of the invention, the constituent components may include sulfhemoglobin (claim 18). Then, the method further comprises selecting a radiation wavelength within the range of 615 to 625 nanometers for inclusion in the absorbance subset as the radiation wavelength for the measurement of sulfhemoglobin, and preferably 621.7 nanometers (claim 19).

The method of the present invention further includes correcting the calculated concentrations of constituent components for the effects of light scattering by red blood cells (claim 20). This correction includes correcting the calculated concentrations of constituent components as a function of the relative concentrations of the constituent components (claim 21), and may include iteratively determining a red blood cell scattering vector for the particular composition of the whole blood sample being analyzed; and using the red blood cell scattering vector to correct the calculated constituent component concentrations (claim 22).

The method of the present invention further includes correcting the calculated constituent component concentrations for the effects of non-specific light scattering (claim 23). This correction includes correcting the calculated concentrations of constituent components as a function of the relative concentrations of the constituent components (claim 24), and may include iteratively

determining a non-specific scattering vector for the particular composition of the whole blood sample being analyzed; and using said non-specific scattering vector to correct the calculated constituent component concentrations (claim 25).

Another aspect of the method simultaneously corrects the calculated concentrations of constituent components for the effects of light scattering by several scattering factors (claim 40), including light scattering by red blood cells and non-specific light scattering (claims 26 and 44).

Yet another feature of the present invention is the correction of the calculated concentrations of constituent components as a function of wavelength (claims 34-36).

In more general terms, the present invention determines the concentrations of a plurality of k constituent components of unaltered whole blood, where k is an integer. A plurality of n different substantially monochromatic radiation wavelengths are generated, where n is an integer and n > k. Further, k of the n wavelengths are selected primarily to measure radiation absorption by the k constituent components, and n - k of the n wavelengths are selected to compensate for errors due to n - k scattering factors in unaltered whole blood. After the radiation wavelengths are generated, a sample of unaltered whole blood is irradiated with the n radiation wavelengths, and intensities of the n radiation wavelengths are detected after passing through the sample of unaltered whole blood. Finally, the concentrations of the k constituent components of the sample of unaltered whole blood, corrected for the effects of radiation scattering, are calculated as a function of the detected intensities of the n radiation wavelengths (Claim 37).

VI. ISSUES ON APPEAL

1. Whether claims 1, 10, 20-24, 26, 27, 34-36, 37, 41 and 43 are anticipated under 35 U.S.C. § 102(b) in view of Anderson and Sekelj, *Phys. Med. Bio.*, Vol. 12, 2:173-184, 1967 ("Anderson *et al.*").

2. Whether claims 2-9, 11-19, 25, 28-33, 38-40, 42 and 44 would have been obvious under 35 U.S.C. § 103 in view of Anderson *et al.* alone.

3. Whether *res juducata* applies to claims 1, 2, 5, 6, 9-21, 23, 24, 26, 27, 29-36, 37 and 41-43.

4. Whether claims 1, 10, 20-24, 26, 27, 34-36, 37, 41 and 43 would have been obvious under 35 U.S.C. § 103 over Anderson *et al.* and Brown *et al.*, U.S. Patent No. 4,134,678.

5. Whether claims 37-44 have no written description under 35 U.S.C. § 112, first paragraph.

6. Whether claims 1-44 are indefinite under 35 U.S.C. § 112, second paragraph.

7. Whether the amendment filed October 12, 1995 introduced new matter into the disclosure.

VII. GROUPING OF THE CLAIMS

Claims 1-44 are each asserted to be independently patentable.

VIII. ARGUMENT

A. <u>Introduction</u>

In the 42-page Final Office Action mailed March 4, 1996, the fourth Office Action to be issued in this application, the Examiner, for the first time during the prosecution of this case,

objected to the specification under 35 U.S.C. § 112, first paragraph. In addition, the Examiner objected to some of the material introduced with the Amendment filed October 12, 1995 under 35 U.S.C. § 132 as allegedly introducing new matter. The Examiner also rejected claims under 35 U.S.C. § 112, second paragraph. Finally, the Examiner presented four separate bases for rejecting the pending claims under 35 U.S.C. §§ 102 and 103 and under the doctrine of *res judicata*. Appellants respectfully appeal each of the bases for rejecting claims in this application, and present their arguments in more detail in the following sections.

B. <u>The Rejections Based on Prior Art Should be Reversed</u>

1. The eleven declarations strongly support patentability.

As discussed more fully below, the rejection of claims under 35 U.S.C. § 102 is clearly in error and *prima facie* reversible. There are simply no claims in this case that are anticipated by the applied references. Also as discussed more fully below, the rejection of claims under 35 U.S.C. § 103 should be reversed because the prior art does not teach the claimed invention, even if the proposed combination of references were made. On that issue, ten declarations have been filed in this case including, five declarations filed with the Amendment on October 12, 1995, two declarations filed with the Amendment on March 25, 1994, and three declarations filed with the Request for Reconsideration on December 15, 1994. Reference will be made herein to each of these ten declarations. An eleventh declaration is filed herewith to bring the record up to date with respect to the commercial success of the commercial embodiment of the present invention

For completeness, the following table presents each of the eleven declarations, the date they were signed, and their form of citation within this appeal brief.

Declaration	Citation Form
Declaration of Joseph M. Schmitt Under 37 C.F.R. § 1.132, signed February 25, 1994	"Schmitt 2/25/94, ¶ ___"
Declaration of Roland N. Pittman Under 37 C.F.R. § 1.132, signed February 28, 1994	"Pittman, ¶ ___"
Declaration of Gert E. Nilsson Under 37 C.F.R. § 1.132, signed December 8, 1994	"Nilsson, ¶ ___"
Declaration of Per Åke Öberg Under 37 C.F.R. § 1.132, signed December 12, 1994	"Öberg, ¶ ___"
Declaration of A. P. Shepherd Under 37 C.F.R. § 1.132, signed December 12, 1994	"Shepherd 12/12/94, ¶ ___"
Supplemental Declaration of Joseph M. Schmitt Under 37 C.F.R. § 1.132, signed July 10, 1995	"Schmitt 7/10/95, ¶ ___"
Declaration of Charles F. Mountain Under 37 C.F.R. § 1.132, signed July 6, 1995	"Mountain, ¶ ___"
Declaration of Thomas Scecina Under 37 C.F.R. § 1.132, signed July 13, 1995	"Scecina, ¶ ___"
Supplemental Declaration of A. P. Shepherd Under 37 C.F.R. § 1.132, signed August 14, 1995	"Shepherd 8/14/95, ¶ ___"
Declaration of A. P. Shepherd and John M. Steinke Under 37 C.F.R. § 1.131, signed October 4, 1995	"Shepherd and Steinke,¶___"
Second Supplemental Declaration of A. P. Shepherd Under 37 C.F.R. § 1.132, signed October 15, 1996	"Shepherd 10/15/96, ¶___"

Those declarations relate to the issues of patentability in light of the prior art, and significant secondary considerations including licensing of the invention, commercial success, failure of others in the field to arrive at the present invention, despite long felt need, and unexpected results. Those declarations, which will be cited throughout the rest of these remarks, strongly support the patentability of the claims pending in this application.

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2. Secondary considerations strongly support patentability.

a) Commercial success, including licensing the invention, supports patentability.

As reported in Dr. Shepherd's Declaration of August, 1995, Instrumentation Laboratory Company (one of the leading companies in the field, and the assignee of U.S. Patent No. 4,134,678 to Brown *et al.*, which is one of the patents applied by the Examiner in the Final Office Action to reject claims) holds a license to the patent and know-how rights owned by A-VOX Systems, Inc. (the exclusive licensee of The University of Texas System, the owner of the present application) relating to the invention described in the subject patent application. Instrumentation Laboratory Company has the exclusive right to incorporate these patent and know-how rights in the restricted field of non-portable, bench-type products used to measure one or more of the following in unaltered whole blood: bilirubin concentration, total hemoglobin concentration, relative oxyhemoglobin concentration, relative deoxyhemoglobin concentration, relative carboxyhemoglobin concentration, relative methemoglobin concentration or relative sulfhemoglobin concentration. Patent know-how rights are expressly defined in the license to include the information and discoveries described in the present patent application (U.S. Patent Application Serial No. 07/953,680). Shepherd 8/14/95, ¶ 6.

That license specifies a license initiation fee of $50,000, with a minimum royalty over the life of the agreement of over $1,000,000. If sales of the licensed product reach projected levels, the total royalty over the life of the agreement will exceed $11,000,000. Shepherd 8/14/95, ¶ 7.

The Final Office Action, at pages 33 and 35, indicated that the first and second Shepherd Declarations (Shepherd 12/12/94 and 8/14/95) were deemed by the Examiner to be "mute" because the Declarations allegedly did not make clear what the commercial success is attributed to.

Since Examiner Hantis was present at a demonstration of the AVOXimeter 1000 on January 19, 1994, and since a brochure completely describing the functions of that product, and including a picture of the product, was attached to Dr. Shepherd's declaration of 12/94, it is unreasonable for the Examiner to imply (Final Office Action, at page 35), without any support, that the commercial success was somehow due to unclaimed features. In addition, as explained in Dr. Shepherd's supplemental declaration, claim 1 of the present application covers the core functions of the AVOXimeter, and, other than displaying the calculated concentrations, the AVOXimeter 1000 performs no other functions of consequence. Shepherd 8/14/95, ¶ 2. In addition, the subject matter of the license between A-VOX Systems, Inc. and Instrumentation Laboratory Company is the very invention described in the subject patent application. Thus, the required nexus exists between the commercialization of the present invention and the claimed invention because at least claim 1 of the present application covers the entire AVOXimeter 1000, and because the licensed technology is the very technology described in the subject patent application.

In such a situation, "*prima facie* evidence of nexus is established if there was commercial success and if the invention disclosed in the patent was that which was commercially successful." *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991); *see also*, *Dmaco Corp. v. F. Von Langsdorff Licensing Co. Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir.) *cert. denied*, 488 U.S. 956 (1988).

The AVOXimeter continues to enjoy remarkable commercial success. From the beginning of sales in 1993, through the first three quarters of 1996, over 360 units have been sold, which have resulted in accounts receivable of over $2,650,000 for the oximeter and disposable cuvettes.[1]

[1] It should be noted that the disposable cuvettes determines the "depth of said sample chosen to minimize radiation scattering by unaltered whole blood," recited in claim 1.

Shepherd 10/16/96, ¶¶ 2-5. The sales in 1994 represented over 250% of the sales in 1993, the sales in 1995 represented over 110% of the sales in 1994, and the sales for the first three quarters of 1996 represent over 115% of the sales for the entirety of 1995. Shepherd 10/16/96, ¶¶ 2-5.

Thus, it is clear that there are the beginnings of significant sales of products embodying the invention, using only direct mail advertising. Shepherd 8/14/95, ¶¶ 3-5; Shepherd 10/16/96, ¶¶ 2-5. These sales figures and the dramatic increase over a very short time are indicative of the beginnings of a "rush to the invention [that is] probative of non obviousness." *Nicola v. Peterson*, 580 F.2d 898, 914 (6th Cir. 1978) (opinion by Judge Markey, then Chief Judge of the C.C.P.A.).

Such evidence of secondary considerations has great utility in a patentability determination, *Grahm v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), and in fact, "requires a finding of nonobviousness if the matter can be otherwise doubtful," *In re Sernaker*, 702 F.2d 989, 996 (Fed. Cir. 1983) (non-obviousness shown from license of patent not yet issued). In addition, when evidence is submitted to rebut an Examiner's contention of obviousness, the Examiner must start over. Facts established by rebuttal evidence must be evaluated along with facts on which the earlier conclusion of obviousness is reached, not against the conclusion itself. In other words, it is error to review rebuttal evidence solely for its "knockdown ability." *In re Piasecki*, 745 F.2d 1468, 1472-73 (Fed. Cir. 1984); *In re Rinehart*, 531 F.2d 1048, 1052 (C.C.P.A. 1976).

Appellants respectfully assert that this evidence shows remarkable commercial success, which includes not only significant sales of the product embodying the invention, but also the licensing of the invention for substantial royalties, even before a patent has issued. This evidence of commercial success is sufficient to overcome any *prima facie* case of obviousness that the Examiner may have asserted.

b) Failure of others in the industry, long felt need, and unexpected results all support patentability.

It is well established that the failure of others in the field, despite the presence of a long felt need, is strong evidence of non-obviousness, *In re Dow Chemical Corp.*, 837 F.2d 469, 472 (Fed. Cir. 1988) ("Recognition of need, and difficulties encountered by those skilled in the field are classical indicia of nonobviousness."). Such is the case with the present invention.

Specifically, the declarations of Charles F. Mountain and Thomas Scecina, each an expert in the field of blood spectrophotometry, and each a developer of blood co-oximeters for major manufacturers, each independently provide strong evidence of long felt and unsatisfied need.

Mr. Mountain is the co-inventor of U.S. Patent No. 4,134,678 to Brown *et al.*, which is one of the patents applied by the Examiner in the Final Office Action to reject claims. Mountain, ¶ 3. During the five year period preceding the filing of the Brown *et al.* patent application, Mr. Mountain's employer, Instrumentation Laboratory Company,[2] had a team of highly qualified technical experts attempt to design a spectrophotometric device capable of measuring multiple hemoglobin species. One approach taken was to attempt to measure multiple hemoglobin species in unaltered whole blood because this approach offered significant commercial advantages over a system requiring hemolysis. Mountain, ¶ 4.

Those advantages included: (1) lower manufacturing costs, (2) simplification of mechanical and fluidic components by eliminating the processes of hemolysis and dilution, (3) simplification of the calibration of total hemoglobin measurement by eliminating sample dilution, (4) faster analysis, and (5) greater ease of integration with a system for blood gas analysis. *Id.*

[2] As mentioned above in Section VIII.B.2.a, Instrumentation Laboratory Company has taken a license under the present invention.

Mr. Mountain was a member of the design team responsible for developing the spectrophotometric device, and was specifically aware of the teachings of Anderson and Sekelj, *Phys. Med. Bio.*, Vol. 12, 2:173-174, 1967. Mountain, ¶ 5.

Despite years of effort that included numerous experiments with unaltered whole blood in various optical designs and strategies, the Instrumentation Laboratory design team failed in its attempt to devise a means of measuring multiple hemoglobin species directly in unaltered whole blood. Mountain, ¶¶ 7-9. The effort to make measurements directly in nonhemolyzed blood was abandoned at Instrumentation Laboratory, and the spectrophotometric device disclosed in the Brown *et al.* patent was developed. That device, consistent with the disclosure of the Brown *et al.* patent, requires hemolysis prior to the spectrophotometric measurement of multiple hemoglobin species. Mountain, ¶¶ 10-11.

Further, and completely independent of Mr. Mountain, Mr. Thomas Scecina, who was employed by Ciba Corning from 1973 to 1995, also attempted, with a "team of highly qualified scientists and instrument designers," at Ciba Corning to develop a method for measuring multiple hemoglobin species in unaltered whole blood. Scecina, ¶ 5. The reason for attempting such development was that such an instrument would be simpler, faster, and less expensive to manufacture than co-oximeters that hemolyze each blood sample before analyzing it spectrophotometrically. Mr. Scecina concluded that the need for such an instrument was quite evident and long-standing. Scecina, ¶ 5.

Despite the desirability and long-standing need for such a design, Mr. Scecina's design team abandoned their effort to develop the instrument because nothing in their experiments or in the literature indicated that such measurements were feasible at the required accuracies due to the

complex optical properties of unaltered whole blood, and because their experiments indicated that making measurements on unaltered whole blood might be risky and unreliable because the optical behavior of unaltered whole blood was so unpredictable from one sample to the next. Scecina, ¶ 7. Thus, the development effort at Ciba Corning was also abandoned. Scecina, ¶ 7-8.

In addition, Mr. Mountain and Mr. Scecina each find the present invention to produce remarkable and surprising results. Specifically, with reference to Table IV on page 40 of the present application, Mr. Mountain finds it to be "an astonishing accomplishment" that the present invention can make measurements in unaltered whole blood that agree, as closely as they do, with those in hemolyzed blood. Mountain, ¶ 8. Mr. Scecina, like Mr. Mountain, has reviewed the present patent application, including Table IV on page 40, and finds it "quite surprising that the present invention can make measurements in unaltered whole blood that agree so well with those in hemolyzed blood." Scecina, ¶ 12.

Appellants respectfully assert that the existence of long-felt need, the failure of those in the industry to arrive at the invention despite this long-felt need, and the statements by two experienced designers in the industry who work for two of the four major suppliers of products in the field, finding the results accomplished by the invention to be "astonishing" and "surprising," exhibits strong evidence of secondary considerations, and strongly supports the patentability of the presently claimed invention

* * *

In the light of these strong secondary considerations, the patentability of the present invention is clear. Specifically, this evidence shows remarkable commercial success, including not only significant sales of the product embodying the invention, but also the licensing of the

invention for substantial royalties, even before a patent has issued. In addition, the evidence shows the existence of long-felt need, the failure of those in the industry to arrive at the invention despite this long-felt need, and the surprising results achieved by the invention.

Although it is strongly asserted that the Examiner has not established a *prima facie* case of obviousness, the foregoing evidence is strongly persuasive evidence of non-obviousness.

3. The rejections based on Anderson *et al.* should be reversed.

The Examiner has rejected claims 1, 10, 20-24, 26-27, 34-36, 37, 41 and 43 under 35 U.S.C § 102 as being anticipated by Anderson and Sekelj, "Light-Absorbing and Scattering Properties of Non-Haemolyzed Blood," *Phys. Med. Bio.*, Vol. 12, 2:173-184, 1967 ("Anderson *et al.*"), has rejected claims 2-9, 11-19, 25, 28-33, 38-40, 42 and 44 under 35 U.S.C. § 103 as having been obvious in view of Anderson *et al.*, and has rejected claims 1-44 under 35 U.S.C § 103 as being unpatentable over the combination of Anderson *et al.* and Brown *et al.*, U.S. Patent No. 4,134,678 ("Brown *et al.*"). Appellants respectfully traverse each of these rejections. The following subsections are dedicated to a discussion of the Anderson *et al.* reference, and the Brown *et al.* reference is discussed below in Section VIII.B.4.

a) Anderson *et al.* test <u>altered</u> blood of <u>known</u> composition.

Anderson *et al.* do not teach or disclose the claimed invention, and therefore, as a matter of law, cannot anticipate the claimed invention. Further, the Anderson *et al.* publication does not suggest the claimed invention and does not provide any teaching or motivation to make the claimed invention. Accordingly, no *prima facie* case of obviousness has been established.

Independent claim 1 (and <u>all</u> of dependent claims 2-36) of the present application requires the determination of "concentrations of a plurality of constituent components of <u>unaltered whole</u>

blood of unknown composition," (emphasis added). Similarly, independent claim 37 (and all of dependent claims 38-44) requires determination of "concentrations of a plurality of k constituent components of unaltered whole blood," (emphasis added). That is the object and very reason for the Appellants' invention. The Examiner believes that Anderson *et al.* performed measurements of unaltered whole blood of unknown composition. *See, e.g.,* Final Office Action, at page 10, 13, 14 and 16. Such is not the case.

The second paragraph on page 177 of Anderson *et al.* states (with added emphasis): "Fully oxygenated nonhaemolysed red cells suspended in isotonic saline were studied...." Nowhere in the disclosure of Anderson *et al.* is there any teaching of measuring unaltered whole blood, as required by all of the present claims on appeal. The Examiner has been unable to cite any disclosure, teaching or suggestion to the contrary in Anderson *et al.*, despite numerous requests by Appellants for such a reference.

Before suspending nonhemolyzed red blood cells in isotonic saline, Anderson *et al.* must first separate the red blood cells from the other components of whole blood, thus altering the blood sample. This effectively eliminates many of the contributors to light scattering mentioned in the third paragraph on page 7 of the present application, and discussed below in detail in Section VIII.B.3.c. Moreover, by using "fully oxygenated" red cells, the samples used by Anderson *et al.* are of known composition, *i.e.*, oxyhemoglobin (also referred to as HbO_2 in the present application). No other hemoglobin components (deoxy-, carboxy-, met-, or sulfhemoglobin or bilirubin) are present in the samples measured by Anderson *et al.*

Therefore, contrary to the Examiner's interpretation of Anderson *et al.*, Anderson *et al.* measure altered whole blood of known composition. This fact is further borne out by the

declarations of record, all of which are by independent, third-party, well respected researchers in the field. Pittman, ¶ 11; Schmitt 2/25/94, ¶ 11; Nilsson, ¶ 16; Öberg, ¶ 16; Schmitt 7/10/95, ¶6. The Examiner has improperly failed to give those declarations any weight.

b) Anderson *et al.* do not measure concentrations of any components of unaltered whole blood.

As emphasized in the previous section, claims 1-36 require measuring "concentrations of a plurality of constituent components of <u>unaltered whole blood of unknown composition</u>" (emphasis added), and claims 37-44 require measuring "concentrations of a plurality of k constituent components of <u>unaltered whole blood</u>," (emphasis added). In contrast, also as noted above, each of the measurements taken by Anderson *et al.* are taken on "red-cell suspensions," which, in accordance with the second paragraph on page 177 of Anderson *et al.*, means that only fully oxygenated non-hemolyzed red cells suspended in saline were studied.

In fact, the legends of each of the graphs depicted in the figures of the Anderson *et al.* article, with the exception of Figure 5, expressly state that what was being studied were "red cell suspensions," and it is quite likely that the measurements depicted in Figure 5 were also taken from red-cell suspensions. Schmitt 7/10/95, ¶ 6.

Although Anderson *et al.* disclose that the difference in total optical attenuation before and after hemolysis of a particular red-cell suspension in saline is a rough estimate of the magnitude of light scattering before that particular blood suspension was hemolyzed (Schmitt 7/10/95, ¶4), there is absolutely no disclosure in Anderson *et al.* of measuring unaltered whole blood of unknown composition for any purpose. The Examiner's conclusion to the contrary is simply wrong. Further, she has not cited any relevant portion of Anderson *et al.*

That Anderson *et al.* does not ever measure unaltered whole blood is further emphasized by the fact that curve C in Figure 6 of Anderson *et al.* indicates that the magnitude of light scattering varies with total hemoglobin concentration. Thus, the only way to use the disclosure of Anderson *et al.* to "correct" for the effects of scattering when measuring a sample of unaltered whole blood, as erroneously contended by the Examiner (Final Office Action, at pages 11 and 14), is first to measure the total hemoglobin concentration of the sample under test by some independent method. Schmitt 7/10/95, ¶ 4. This prior measurement would thus render any sort of measurement by the apparatus disclosed in Anderson *et al.* completely superfluous, and thus useless. In addition, this prior independent measurement would render the sample of "known" composition, contrary to the requirements of the presently claimed invention. Schmitt 7/10/95, ¶4.

Moreover, it is clear that Anderson *et al.* do not perform any tests on unaltered whole blood because Anderson *et al.*, while measuring the scattering characteristics of red blood cells suspended in saline, do not measure the scattering effects present in unaltered whole blood, which are measured by the present invention. Such unaltered whole blood includes red blood cells suspended in plasma, and the plasma includes many constituents other than red blood cells. Schmitt 7/10/95, ¶ 7. The following section, with its subsections, explains why Anderson *et al.* do not, and in fact are incapable of, making meaningful measurements of the concentrations of the constituent components of unaltered whole blood, because Anderson *et al.* do not account for any of the scattering factors present in unaltered whole blood -- scattering factors that are accommodated only by the present invention.

c) **Anderson *et al.* do not contemplate scattering correction.**

Independent claim 1 of the present application requires the generation of a plurality of radiation wavelengths, the plurality of wavelengths including an absorbance subset that has been selected by its ability to distinguish the constituent components of unaltered whole blood of unknown composition, and having been selected to minimize the effects of radiation scattering and to maximize radiation absorbance by these constituent components. That plurality of wavelengths, as further defined in claim 1, also includes a scattering subset of wavelengths that has been "selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance by unaltered whole blood." Similarly, claim 37 requires the generation of n - k wavelengths that have been "selected to compensate for errors due to n - k scattering factors in unaltered whole blood." In other words, some of the radiation wavelengths generated by the present invention are specifically selected for, and dedicated to, the purpose of correcting for the effects of radiation scattering.

Claims 1 and 37 also require calculating the concentrations of the plurality of constituent components of the sample of unaltered whole blood, corrected for the effects of radiation scattering, as a function of detected intensities of all of the radiation wavelengths, including those dedicated to scattering correction. Dependent claims 20-36 and 38-40 expand on the details of correction for the effects of radiation scattering.

The Examiner relies on the last line of the first paragraph from page 180 of Anderson *et al.* for the proposition that Anderson *et al.* allegedly contemplate correction for scattering. Final Office Action, at pages 11 and 14.

The Examiner's understanding of Anderson *et al*, however, is fundamentally incorrect, and that may have misled the Examiner to speculating that Anderson *et al.* can accurately deduce the magnitude of light scattering produced by an unknown sample of whole blood from measured optical density values and known extinction coefficients of the hemoglobin species under consideration. But Anderson *et al.* cannot.

The relevant statement on page 180 of Anderson *et al.* shows that key aspects of the presently claimed invention were completely unknown to Anderson *et al.* Specifically, the Examiner's reliance on the statement from page 180 of Anderson *et al.* is completely misplaced since the statement does not account for:

- the sample-to-sample variation in light scattering in whole blood due to the eight factors described on page 7, paragraph 3 of the present application; or
- the hemoglobin species-dependence of the scattering vectors described on page 7, paragraph 2 of the present application; or
- the wavelength dependence of the scattering vectors described on page 7, paragraph 1 of the present application; or
- the fact that there are actually at least two independent scattering vectors to be found when whole blood is illuminated, as described on pages 20-30 of the present application.

In accordance with the presently claimed invention, it is the generation of the scattering subset of wavelengths, in addition to the absorbance subset of wavelengths, that permits the presently claimed invention to correct for errors introduced in the determination of the

concentrations of the constituent components of unaltered whole blood of unknown composition. Such correction is nowhere contemplated by Anderson *et al.*, as explained in more detail in the following subsections.

(1) Light scattering in unaltered whole blood samples is unpredictable from one sample to another.

As mentioned in the third paragraph on page 7 of the present application, there are at least eight uncontrolled factors identified that make light scattering in whole blood samples unpredictable from one sample to another. These are: 1) the different plasma protein concentrations that determine the refractive index of plasma in one sample versus another; 2) the aggregation of red blood cells in the sample; 3) the different hemoglobin concentrations inside the red cells that alter their refractive index; 4) the size and shape of the red blood cells; 5) chylomicrons or other light-scattering lipid particles; 6) cell fragments; 7) microscopic clots; and 8) light-sieving effects of sedimented red blood cells. Schmitt 2/25/94, ¶¶ 10, 12, 14; Pittman, ¶¶ 10, 12, 14; Öberg, ¶ 11; Nilsson, ¶ 11; Schmitt 7/10/95, ¶¶ 7-14.

In trying to back-calculate hemoglobin concentrations from measured optical densities of whole blood for an unknown sample of whole blood, one cannot first adjust the parameters in Twersky's equation (the equation used by Anderson *et al.*) to fit the data and then turn around and subtract off the scattering term to determine the part due to absorbance by hemoglobin, yet this is what would have to be done even to attempt to apply Twersky's theory in the manner suggested by the Examiner. Schmitt 2/25/94, ¶ 9; Pittman, ¶ 9; Nilsson, ¶ 12; Öberg, ¶ 12. Furthermore, the Twersky formalism used by Anderson *et al.* describes "ideal" whole blood, and does not even include provisions for dealing with red cell aggregation, chylomicrons, cell fragments, and other uncontrolled factors that cause light scattering in real whole blood samples. Schmitt 2/25/94, ¶ 10;

Pittman, ¶ 10; Nilsson, ¶ 11; Öberg, ¶ 11. Moreover, as mentioned above in Section VIII.B.3.a. Anderson *et al.* perform measurements on simplified "ideal" whole blood in the form of oxygenated red cells suspended in isotonic saline.

(2) Light scattering in unaltered whole blood samples depends in a complicated way on the particular hemoglobin species present in the sample under consideration.

In the second paragraph on page 7 of the present application, it is pointed out that the total contribution to the optical absorbance of whole blood due to light scattering depends in a complicated way on the actual hemoglobin species present in the sample under consideration. For example, the sample may be comprised purely of oxyhemoglobin or 50% oxyhemoglobin and 50% carboxyhemoglobin, or the sample may be comprised of any combination of the possible hemoglobin species. An untutored reading of Anderson *et al.* (namely that the contribution to unaltered whole blood's optical absorbance which is due only to light scattering is determined by path length, total hemoglobin concentration, and detecting geometry) would not allow for the dependence of light scattering on the particular hemoglobin species present in the given sample.

The presently claimed invention, by generating a scattering subset in addition to an absorbance subset of wavelengths (claims 1 and 37), makes a quantitative correction for the light scattering of each unknown blood sample as a function of the particular hemoglobin species it contains (also see Figures 4 and 5 of the present application, and supporting text). That correction is expressly defined in claims 21, 24, 27 and 43 (and claims 22, 25 and 28-33 dependent therefrom). The passage cited by the Examiner from page 180 of Anderson *et al.* demonstrates that Anderson *et al.* were completely unaware of the necessity of having a hemoglobin-species-dependent scattering vector.

(3) Light scattering in unaltered whole blood depends in a complicated way on the wavelength of the impinging light.

Appellants explain in the first paragraph on page 7 of the present application, that the total contribution to the optical absorbance of whole blood due to light scattering depends in a complicated way on the wavelength of the impinging light. In the passage cited by the Examiner from page 180 of Anderson *et al.*, it is stated that "scattering remains the same for this sample depth and haemoglobin content when wavelength is varied." That assertion is patently false as the data of Pittman clearly shows. *See*, Figure 3 of the present application; Nilsson, ¶ 11; Öberg, ¶ 11. In contrast to this misconception of Anderson *et al.*, the present invention makes a quantitative correction for the light scattering of each unknown blood sample (claims 1 and 37), specifically by employing scattering vectors that vary with wavelength (claims 34, 35 and 36). The passage cited by the Examiner demonstrates that Anderson *et al.* were completely unaware of the necessity or utility of using wavelength-dependent scattering vectors.

(4) There are actually at least two independent scattering vectors to be found when unaltered whole blood is illuminated.

Pages 20-30 of the present application describe both a red blood cell scattering vector and a nonspecific scattering vector. Claims 20, 23, 26 and 44 (and claims 21, 22, 24, 25 and 27-36 dependent therefrom) are specifically directed to those features. Both vectors are important in making accurate measurements of the concentrations of hemoglobin species in unaltered whole blood. There is no hint of two or more forms of scattering in Anderson *et al.*, or in Twersky's theory used by Anderson *et al.* Therefore, the innovation of these two independent scattering

vectors as disclosed and claimed in the present application is original and could not have been deduced from Anderson *et al.*

* * *

In rejecting claims 1, 10, 20-24, 26, 27, 34-36, 37, 41 and 43 under 35 U.S.C. § 102(b) as anticipated by Anderson *et al.*, the Examiner asserts that "Anderson inherently has correction" for light scattering (Final Office Action, at pages 11 and 14). The foregoing discussion demonstrates that the only "correction" that Anderson *et al.* have is merely a fixed quantity that fails to take into account the eight or more uncontrolled factors that make the magnitude of light scattering unpredictable from one sample of whole blood to the next, that fails to contemplate a scattering subset of wavelengths to accommodate those uncontrolled factors (claim 1), that fails to treat the wavelength dependence of the light scattering (claims 34, 35 and 36), that does not account for the variation of the magnitude of light scattering from one blood sample to another (claims 22 and 25), that does not account for the dependence of the magnitude of light scattering on the particular hemoglobin species present in the sample (claims 21, 22, 24, 25 and 27-33), and that does not include either of the scattering vectors of the presently claimed invention (claims 20-36). For these reasons, Appellants respectfully request the reversal of the rejection of claims 1, 10, 20-24, 26, 27, 34-36, 37, 41 and 43 as being anticipated by Anderson *et al.*

4. The rejections based on Brown *et al.* should be reversed.

The Examiner has rejected claims 1, 10, 20-24, 26, 27, 34-36, 37, 41 and 43 in this application as being unpatentable over the teachings of Anderson *et al.* in view of Brown *et al.*, U.S. Patent No. 4,134,678. In light of the comments in the following subsections, Appellants respectfully request reversal of this rejection.

a) Brown *et al.* alter the blood sample by hemolysis.

The Brown *et al.* reference does not supply any of the discrepancies existing in the Anderson *et al.* reference, presented above in Section VIII.B.3. In particular, the Brown *et al.* reference presents multi-wavelength spectrophotometry which uses one wavelength for each blood component to be determined. Brown *et al.*, Figure 5; col. 3, lines 31-39; Schmitt 7/10/95, ¶ 16.

The only scattering correction contemplated by Brown *et al.* is accomplished by hemolyzing the blood sample before optical measurements are made. See Brown *et al.*, col. 6, lines 41-43; col. 8, lines 2-4 and 21-22; col. 10, lines 8-9; col. 13, lines 55-68; col. 14, lines 16-17; col. 15, line 43; col. 16, lines 8 and 40; col. 17, lines 6 and 37; and col. 18, lines 9 and 36-37. Schmitt 7/10/95, ¶ 17; Mountain, ¶¶ 11, 13.

Thus, in striking contrast to the presently claimed invention, Brown *et al.* do not disclose or suggest the measurement of unaltered whole blood, and thus cannot supply the above-noted discrepancies in the Anderson *et al.* reference.

b) Brown *et al.* do not provide scattering correction.

As emphasized time and time again during the prosecution of this application, in accordance with independent claim 1 of the present application, the generation of a plurality of wavelengths is required, the plurality of wavelengths including an absorbance subset and a scattering subset. Independent claim 37 requires the generation of n radiation wavelengths in order to measure k blood components, where n and k are integers and n > k. In striking contrast, the Brown *et al.* reference uses one wavelength for each blood component to be determined (*see*, Figure 5 in col. 3, lines 31-39), and uses <u>no other wavelengths</u>. There is no disclosure or suggestion of a scattering subset of wavelengths, as required by the present claims. Schmitt 7/10/95, ¶ 16.

c) A co-inventor of the Brown *et al.* invention knows the Examiner is wrong.

Charles F. Mountain is a named co-inventor of the Brown *et al.* patent. The declaration of Mr. Mountain under 37 C.F.R. § 1.132, refutes completely the Examiner's conclusion that the presently claimed invention would have been obvious in light of the combined teachings of Anderson *et al.* and Brown *et al.* Mountain, ¶ 12.

In particular, Mr. Mountain states that Anderson *et al.* do not present a practical system to determine concentrations of hemoglobin species in unaltered whole blood for several reasons. First, Anderson *et al.* require the measurement of optical density before and after hemolysis. Second, since light scattering may vary markedly from one clinical blood sample to the next, this would render completely impractical the use of the Anderson *et al.* system to "correct" for scattering. Mountain, ¶ 14.

Mr. Mountain also observes that the Brown *et al.* patent requires hemolysis prior to spectrophotometric measurements (Mountain, ¶ 11), and in the over 28 years since the Anderson *et al.* paper was published, and in the over 16 years since the Brown *et al.* patent was issued, all companies that have developed co-oximeters that measure total hemoglobin concentration produced instruments that hemolyze the sample before subjecting the sample to spectrophotometric analysis. Mountain, ¶ 15.

* * *

For these reasons, the rejection of claims based upon the teachings of Brown *et al.* should be reversed.

5. Each of claims 1-44 is independently patentable.

In light of the foregoing comments, Appellants respectfully assert that the Anderson *et al.* reference does not render any of claims 1-44 unpatentable, either alone, or in combination with the Brown *et al.* reference.

Specifically, none of the cited prior art determines the constituent components of unaltered whole blood of unknown composition, using the recited wavelengths of substantially monochromatic radiation in an absorbance subset and in a distinct scattering subset. In addition, there is no disclosure of a selection of sample depth, detection area, and detection distance from the sample, as required by claim 1. Dependent claims 2-36 are asserted to be patentable for the same reasons asserted with respect to claim 1, and for the additional detail recited therein as presented in more detail below.

In particular, there is no disclosure or suggestion in the prior art of any way to arrive at the mechanical dimension ranges, and specific mechanical dimensions for the sample depth, detecting area, distance from the sample to the detector, and range of radiation half-angle, as specifically required by each of claims 2-9.

There is also no suggestion in the applied prior art for correcting the calculation of concentrations of components for the effect of finite spectral bandwidth, as required by claim 10.

Next, the prior art of record does not contemplate the selection of four radiation wavelengths by calculating error indices, and by selection of a quadruple of radiation wavelengths having minimum error indices, as required by claim 11, nor is there any disclosure or suggestion of the range for the four wavelengths, required by claim 12, or the specific wavelength quadruples required by claims 13, 14 and 15.

The applied prior art also does not disclose or suggest the measurement of bilirubin using the recited range in claim 16, or using the specific wavelength of claim 17. Similarly, the prior art does not disclose or suggest the measurement of sulfhemoglobin, using the wavelength range specified by claim 18, or the specific wavelength specified by claim 19.

Turning now to the particulars of the scattering correction, there is no disclosure or suggestion in the applied prior art of correcting calculated concentrations for the effects of light scattering by red blood cells, as required by claim 20, or for the effects of non-specific light scattering, as required by claim 23, or for the effects of both as required by claim 26. Further, there is no disclosure or suggestion of correcting for scattering as a function of the relative concentrations of the constituent components, as required by claims 21, 24 and 27, or for the iterative determination of the red blood cell scattering vector or non-specific scattering vector, or both scattering vectors as required by claims 22, 25 and 28.

Claims 29-33 each depend, either directly or indirectly, from claim 28, and add limitations similar to those of claims 11, 12, 16 and 18 (each of which depend either directly or indirectly from claim 1). However, claim 29-33 are each asserted to be independently patentable.

In addition, none of the applied prior art contemplates the correction of the calculated concentrations as a function of wavelength, as required by claims 34, 35 and 36 (each of which have different dependencies).

Independent claim 37 requires the determination of k components of <u>unaltered whole blood</u>, by irradiating a sample of unaltered whole blood with n radiation wavelengths where n and k are integers and $n > k$. Further, k of the n wavelengths have been chosen primarily to measure absorption by the k components, and the remaining $n - k$ wavelengths have been chosen to

compensate for the effects of scattering factors in unaltered whole blood. As emphasized above, none of the prior art measure unaltered whole blood, and none use additional radiation wavelengths to compensate for scattering factors in unaltered whole blood. Dependent claims 38-44 are also patentable for these reasons, and for the additional detail recited therein.

Specifically, there is no suggestion in the prior art of record for the calculation of the concentrations of the k components of unaltered whole blood using a set of n linear equations that equate a vector of n optical densities with a linear combination of k light absorbance vectors and n - k light scattering vectors, as required by dependent claim 38, or for each of the k light absorbance vectors corresponding to a specific one of the k constituent components, the entries of each light absorbance vector being extinction coefficients of a corresponding constituent component at each of the n wavelengths, as required by dependent claim 39.

In addition, the prior art of record does not disclose the iterative determination of scattering vectors as functions of the composition of the unaltered whole blood sample under analysis, as recited in dependent claims 40 and 44.

There is no suggestion in the prior art of record for the correction of the calculated concentrations of the k constituent components for the effects of finite spectral bandwidth of the n wavelengths, as required by dependent claim 41, or for the correction of the calculated concentrations of the k constituent components as a function of the relative concentrations of the k constituent components, as required by dependent claim 43.

Finally, the prior art of record does not contemplate the selection of four radiation wavelengths by computing an error index for each of HbO_2, HbCO and Hi as the sum of the absolute values of the errors that are induced in the measurement of relative concentrations of

HbO_2, HbCO and Hi due to a change in optical density measurements, and the selection of a quadruple of radiation wavelengths having minimum error indices, as required by dependent claim 42.

6. The rejections based on *res judicata* should be reversed.

The Examiner has rejected 1, 2, 5, 6, 9-21, 23, 24, 26, 27, 29-36, 37 and 41-43 under the doctrine of *res judicata* in light of the decision in the appeal of parent application Serial No. 07/313,911. Appellants respectfully request the reversal of this rejection as presented in detail in the following sections.

a) *Res judicata* cannot apply because the issues are different.

The C.C.P.A. has consistently held that the doctrine of *res judicata* is proper only when the issues are the same. *See In re Herr*, 377 F.2d 610, 611 (C.C.P.A. 1967) (holding that if the specifications are materially different then the issues are different); *In re Fried*, 312 F.2d 930, 931 (C.C.P.A. 1963) (holding that if the claims are materially different then the issues are different). The Supreme Court stated this essential principle in *Commissioner of Internal Revenue v. Sunnen*, 333 U.S. 591, 597-98 (1948):

> The general rule of *res judicata* applies to repetitious suits involving the same cause of action. It rests upon considerations of economy of judicial time and public policy favoring the establishment of certainty in legal relations.

The C.C.P.A., stating the same essential principle, observed that "the issues must be identical before *res judicata* is applicable." *In re Fried*, 312 F.2d at 932 n.3. As shown below, the present case involves neither the same application nor identical issues and *res judicata* was therefore improperly applied by the Examiner.

b) Different claims are different issues.

In re Fried addressed the impact of a difference in the claims between a parent application and a CIP application -- exactly the same situation as in the present case. The Board of Appeals had affirmed an examiner's rejection of claims in a CIP based on *res judicata* from an earlier final rejection in the parent application. In reversing the Board, the court observed that "[t]o a person skilled in this art it is readily apparent that [the] claims ... of the parent application are broader than the appealed claims. ... The issue here is, therefore, a different issue than that decided [earlier]." *In re Fried*, 312 F.2d at 932; *see also In re Craig*, 411 F.2d 1333, 1336 (C.C.P.A. 1969) ("there exists sufficient technical ground for not applying *res judicata* in that the claims here on appeal are substantially different from the claims in the parent application").

In the present case, the claims in the parent application are, similarly, broader than the claims of the present CIP. For example, claim 1 of the present application is distinguishable from the corresponding claim 1 of application Serial No. 07/313,919. Claim 1 presently under examination requires the step of generating a plurality of radiation wavelengths, including an absorbance subset of wavelengths that has been selected by its ability to distinguish the constituent components, to minimize the effects of radiation scattering and to maximize radiation absorbance by the constituent components. Also included among the plurality of generated wavelengths is a scattering subset of wavelengths that has been selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance by unaltered whole blood. Claim 1 presently under examination also requires the calculation of concentrations of the plurality of constituent components, corrected for the effects of radiation scattering, based upon detected intensities of each of the plurality of wavelengths, including each of the absorbance

subset of wavelengths and scattering subset of wavelengths. In a similar fashion, independent claim 37 requires the measurement of n blood components using k radiation wavelengths, where n and k are integers and n > k. As further stated in claim 37, n - k of the wavelengths are selected to compensate for n - k scattering factors in unaltered whole blood.

In contrast, the claims on appeal in application Serial No. 07/313,919 required only the generation of a plurality of radiation wavelengths, without requiring a subset of those wavelengths to be an absorbance subset of wavelengths selected according to specified criteria, and without requiring a distinct scattering subset of wavelengths, selected according to different specified criteria. In addition, claim 1 on appeal in Serial No. 07/313,919 did not include a scattering subset of wavelengths.

To further emphasize the distinctions between claim 1 presently under examination, and claim 1 on appeal in application Serial No. 07/313,919, Appellants present, in tabular form, the first and last elements of each claim.

FIRST AND LAST ELEMENTS OF CLAIM 1 UNDER EXAMINATION	FIRST AND LAST ELEMENTS OF CLAIM 1 ON APPEAL IN SERIAL No. 07/313,919
generating a plurality of substantially monochromatic radiation wavelengths, each wavelength of an absorbance subset of said plurality of wavelengths having been selected by their ability to distinguish the constituent components and having been selected to minimize the effects of radiation scattering and to maximize radiation absorbance by said constituent components, and each wavelength of a scattering subset of said plurality of wavelengths having been selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance by unaltered whole blood;	generating a plurality of radiation frequencies each determined to distinguish one said constituent component from another said constituent component, and to minimize the effect of radiation scattering and to maximize radiation absorbance by whole, undiluted blood;
calculating concentrations of said plurality of constituent components of said sample of unaltered whole blood corrected for the effects of radiation scattering, based upon detected intensities of each of said plurality of radiation wavelengths, and based upon predetermined molar extinction coefficients for each of said constituent components at each of said plurality of radiation wavelengths.	calculating concentrations of each of at least three said constituent components of said sample of whole, undiluted blood, based upon detected intensities of said radiation frequencies, and upon predetermined molar extinction coefficients for each of said constituent components at each of said radiation frequencies.

Similarly, independent claim 37 and the claims of the parent application are also different. Since the claims of the CIP application presently on appeal are narrower than those of the parent application, the issues are different and the doctrine of *res judicata* is not appropriate.

c) Different specifications are different issues.

In re Herr addressed the impact of a difference in the disclosures between a parent application and a CIP application. The court pointed out that the issue before it was whether or not the claims should be allowed in view of the application and record currently before the court. *In re Herr*, 377 F.2d at 611. The court then held that although "the present claims are identical to those sought to be patented earlier[,]" *Id.* at 612 n.5 (emphasis added), the fact that the CIP contained additional disclosure and was supported by additional affidavits rendered the issues different. The court, therefore, held that *res judicata* was improper. *Id.* at 610-12.

In the present case, the CIP application contains additional disclosure relating to the selection of radiation wavelengths and the processing of the measurements to calculate concentrations of the constituent components of whole undiluted blood. In addition, as mentioned in Section VIII.B.1. above, eleven declarations have been presented in the present case that were not in the record when the prior appeal was determined. Here, as in *In re Herr*, this information is directed to the discrepancies noted by the Board of Appeals when it rejected the parent application. The issues are, therefore, different and the application of *res judicata* is improper.

d) The issue was not actually and necessarily litigated.

"[W]here the second action between the same parties is upon a different cause or demand, the principle of *res judicata* is applied much more narrowly. In this situation, the judgment in the prior action operates as an estoppel, not as to matters which might have been litigated and determined, but 'only as to those matters in issue or points controverted, upon the determination of which the finding or verdict was rendered.'" *Commissioner of Internal Revenue*, 333 U.S. at 597-98 [citation omitted].

Although referred to as *res judicata* in *Commissioner of Internal Revenue*, the above-mentioned estoppel is commonly referred to as "issue preclusion." The Federal Circuit has crystallized the requirements for issue preclusion in *In re Freeman*, 30 F.3d 1459, 1465 (Fed. Cir. 1994):

> Issue preclusion is appropriate only if: (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) plaintiff had a full and fair opportunity to litigate the issue in the first action.

The second requirement is not satisfied in this case since the Board of Appeals, in its decision on the parent application, never addressed the question of whether the claims as modified

in this CIP application would be allowable. The Board would have had to anticipate and reject the additional disclosure, the eleven additional declarations, the narrower claims of the CIP, and the extensive additional disclosure of the CIP. To the contrary, the Board's prior decision repeatedly stressed that the specification of the parent application failed to disclose sufficient detail, implying that subsequent disclosures might remedy the omissions. See, Decision of the Board of Patent Appeals and Interferences, Appeal No. 92-0991, at pages 5, 6, 9, 10 and 13. It is this detail that the CIP application provides. In particular, the CIP application adds extensive disclosure relating to improving the calculation of the concentrations of the constituent components, including, for example, the correction of the calculation for the deleterious effects of radiation scattering.

Further, arguably these requirements could never be met in the present case. If the Board had anticipated the additional disclosure, the eleven declarations and the narrower claims of the CIP, then the Board would have been addressing an issue that was not "essential to a final judgment" on the parent application. The third requirement would therefore be left unsatisfied and the Board's decision would not carry any preclusive effect.

e) *Res judicata* cannot stand alone.

If the other rejections are overturned, then the *res judicata* rejection cannot stand on its own. *In re Kaghan*, 387 F.2d 398, 401 (C.C.P.A. 1967); *In re Craig*, 411 F.2d 1333, 1336 (C.C.P.A. 1969); also *see* MPEP § 706.03(w).

MPEP § 201.07 provides, in pertinent part, for the right to file a continuation:

> The continuation application may be filed under ... 37 C.F.R. § 1.62. ...
> At any time before the ... termination of proceedings on his or her earlier application, an applicant may have recourse to filing a continuation in order to ... establish a right to further examination by the primary examiner.

37 C.F.R. § 1.197(c) provides that "[t]he date of termination of proceedings is the date on which the time for appeal to the court ... expires." For the parent application, that date was September 30, 1992. Since the present CIP application was filed on September 29, 1992, Appellants have established a "right to have that application examined." *In re Kaghan*, 387 F.2d at 401.

This right to an examination is not satisfied by a *res judicata* rejection. *In re Kaghan*, 387 F.2d at 401 ("holding of *res judicata* without reliance on any other ground of rejection is not an examination on the merits"); *see also In re Craig*, 411 F.2d at 1336 (quoting *In re Kaghan* with approval). The *Kaghan* court declared that the Patent Office had "waived [its] right to apply a *res judicata* rejection in these circumstances." *In re Kaghan*, 387 F.2d at 401. In these decisions, the C.C.P.A. seemed to be implying that if there are no other grounds for rejection (aside from *res judicata*), then the issues <u>cannot</u> be the same.

The *Kaghan* Court went on to declare that "[t]his analysis is completely consistent with MPEP 706.03(w)[.]" *In re Kaghan*, 387 F.2d at 401. Against the argument that the MPEP does not enjoy the force of law, the court reiterated its holding that "'the express provisions of MPEP set forth an established Patent Office policy on which Appellants for patents are entitled to rely in good faith[.]'" *Id.* [citation omitted].

* * *

The issue in the present case is, as pointed out in *In re Herr*, whether the claims should be allowed in view of the application and record currently before the Patent Office. Both the claims and the specification are materially different in the present CIP application from those of the parent application, and substantial additional evidence supporting patentability has been introduced by declaration. Any one of these conditions alone would compel the conclusion that the CIP application and the parent application present different issues; the fact that all three conditions exist

only makes that conclusion even stronger. Since the issues are different, the doctrine of *res judicata* cannot be applied. Moreover, if the other grounds for rejection are overcome, then it is not even necessary to address the merits of the *res judicata* rejection since it cannot stand on its own.

C. The Objection to the Specification and Rejection of claims 37-44 under 35 U.S.C. § 112, First Paragraph, Should be Reversed

In the objection to the specification (Final Office Action, at pages 2-4), the Examiner states that she can find no written description in the specification for the generation of a plurality of substantially monochromatic radiation wavelengths which are divided into two subsets: an absorbance subset of wavelengths and a scattering subset of wavelengths. In addition, the Examiner alleges that there is no written description for claims 37 and 38. Using this unfounded assertion that there is no literal support for these claimed elements, the Examiner objects to the specification under 35 U.S.C. § 112, first paragraph, and rejects claims 37-44. Among these claims, only claims 37 and 38 are specifically identified as allegedly not complying with § 112, claims 39-44 presumably being rejected because they depend from a rejected claim. No other claims are rejected on these grounds.

In light of the comments in the following subsections, Appellants respectfully request reversal of this rejection.

1. There is no requirement that claim language appear *in ipsis verbis* in the specification.

The Examiner is apparently construing the requirements of 35 U.S.C. § 112, first paragraph to require literal correspondence between the claims and the specification. That is not and never has been the law. In fact, it is well established that "the invention claimed does not have to be

described *in ipsis verbis* in order to satisfy the description requirement of [35 U.S.C.] § 112." *In re Wertheim*, 541 F.2d 257, 265 (C.C.P.A. 1976).

As pointed out below, the original specification fully satisfies the requirements of all of the sections of 35 U.S.C. § 112, and the Examiner's objection to the specification and rejection of claims is unfounded.

2. The original specification provides support for claims 37-44.

The specification of the subject patent application, as originally filed, provides full and complete disclosure the generation of a plurality of substantially monochromatic radiation wavelengths, each wavelength of an absorbance subset of the plurality of wavelengths having been selected by their ability to distinguish the constituent components, and each wavelength of a scattering subset of the plurality of wavelengths having been selected to maximize the effects of radiation scattering relative to the effects of absorbance at the scattering wavelengths.

In particular, the original specification describes, at page 9, line 25 through page 10, line 2, that, in one embodiment of the invention, seven wavelengths are generated, six wavelengths having been selected to measure the concentrations of oxyhemoglobin, carboxyhemoglobin, methemoglobin, reduced hemoglobin, sulfhemoglobin and bilirubin, and the seventh wavelength "is chosen from that part of the spectrum where absorbance by bilirubin and each of the five hemoglobin species is as small as possible in comparison with the effects of light scattering." This provides clear support for the generation of seven wavelengths, six forming an absorbance subset of wavelengths, and one forming a scattering subset of wavelengths.

In addition, in the original specification, at page 20, lines 24-29, it is explained that

> "n measuring wavelengths are employed to measure k constituent components, with n > k, thereby creating an overdetermined system of equations with respect to the

chemical compounds being measured. The n - k extra equations provide a means by which errors due to n - k scattering factors can be compensated."

In other words, in order to measure k components, n measuring wavelengths are employed, k of the n wavelengths forming an absorbance subset of wavelengths, and n - k wavelengths forming a scattering subset of wavelengths. It is this language of the specification, in combination with the language of claim 1 as originally filed, that provides virtually literal support for independent claim 37.

Next, in the paragraph spanning pages 23 and 24 of the original specification, embodiments A and B are discussed, each of which require the generation of seven wavelengths. In embodiment A, six of the seven wavelengths form an absorbance subset of wavelengths and are used to measure the concentrations of the six blood components HbO_2, HbCO, Hi, Hb, SHb and br, and the seventh wavelength forms a scattering subset of wavelengths used to correct for light scattering by red blood cells. Thus, in embodiment A, n is seven, k is six, and n - k is one

As also explained in the same paragraph, in embodiment B, five of the seven wavelengths form an absorbance subset of wavelengths and are used to measure the concentrations of the five blood components HbO_2, HbCO, Hi, Hb and br, and two of the seven wavelengths form a scattering subset of wavelengths used to correct for nonspecific light scattering, and to correct for light scattering by red blood cells. Thus, in embodiment B, n is seven, k is five, and n - k is two.

Finally, in the paragraph spanning pages 34 and 35, embodiment C is described which uses eight wavelengths, six of the eight wavelengths forming an absorbance subset of wavelengths used to measure the concentrations of the six blood components HbO_2, HbCO, Hi, Hb, SHb and br, and the seventh and eighth wavelengths forming a scattering subset of wavelengths used to correct for

the effects of red blood cell scattering and nonspecific scattering. Thus, in embodiment C, n is eight, k is six, and n - k is two.

Turning now to dependent claim 38, recited is the calculation of a vector of n optical densities, and the use of these optical densities in a set of n linear equations to calculate the concentrations of the k constituent components. Claim 38 is supported by the specification as originally filed, for example, at page 20, line 24 to page 21 line 20. There it is explained that n simultaneous equations (shown for example at the top of page 21) are used to solve for the concentrations of the k constituent components. In particular, the concentrations of the k components appear, for example, in the equation on line 16 of page 21.

* * *

In light of these comments, the reversal of the rejection of claims 37-44 under 35 U.S.C. § 112, first paragraph is requested.

3. The amendments to the specification introduced October 12, 1995 did not add new matter.

In the face of an objection to the specification under 37 C.F.R. § 1.117 in the Office Action of April 26, 1995,[3] and in the interest of advancing this case to allowance, Appellants amended the specification with the paper filed October 12, 1995 to include the literal claim language of original claims 1-36.

In particular, the Summary of the Invention was amended to add a paraphrase of each of claims 1-36, and portions of the specification at pages 9, 16, 20, 23 and 35 were amended to reflect the "subset" language appearing in the original claims.

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[3] The 28-page Office Action of April 26, 1995, was the third non-final Office Action issued in this case, and was the first time that the Examiner ever mentioned Rule 117 despite that the originally filed claims had been amended only slightly.

Contrary to the Examiner's position stated in the Final Office Action, at page 4, no new matter was added to the specification because each of the amendments to the specification are fully and completely supported by the claims contained in the application as originally filed. It is well established that the originally filed claims may be considered as part of the original disclosure of the application. *See e.g. McBride v. Teeple*, 109 F.2d 789, 796 (C.C.P.A. 1940).

* * *

In light of the foregoing comments, reversal of the objection to the specification and corresponding rejection of claims 37-44 is respectfully requested.

D. <u>The Rejection of Claims Under § 112, Second Paragraph Should be Reversed</u>

The Examiner has rejected claims 1-44 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner is confused by the fact the absorbance subset of wavelengths, and the various dimensional aspects of the invention, are all selected to <u>minimize</u> radiation scattering, whereas the scattering subset of wavelengths is selected to <u>maximize</u> radiation scattering relative to absorbance at the scattering wavelengths, as recited in claims 1-36. The Examiner also finds confusing the use of the integers, n and k, and the calculation of the difference between these two integers, n - k, as recited in claims 37-44. Appellants respectfully request reversal of these rejections because the claim language is internally consistent, unambiguous, clear, and accurately describes the invention.

In particular, as explained in Section VIII.B.3.c above, the present invention generates a plurality of wavelengths which include an absorbance subset of wavelengths, and a distinct scattering subset of wavelengths. As recited in claims 1-36, and as explained in detail in the

specification, each member of the absorbance subset of wavelengths has been selected by its ability to distinguish the constituent components under consideration, whereas each member of the scattering subset of wavelengths has been selected to maximize radiation scattering relative to the effects of absorbance in order to provide a means to compensate errors due to scattering factors in unaltered whole blood.

Specifically, Appellants refer the Board to the above discussion in Section VIII.C.2. regarding the description of the absorbance subset and scattering subset in the original specification at pages 9-10, 20-21, 23-24 and 34-35.

Thus, the existence of an absorbance subset of wavelengths, the members of which are selected to maximize absorbance relative to radiation scattering, along with a scattering subset of wavelengths, the members of which are selected to maximize the effects of scattering relative to absorbance, is completely compatible.

The Examiner cites page 14, lines 27-34 and page 15, lines 25-31 of the original specification in support of the misperception that "the main purpose of Appellants' device is to minimize the effects of radiation scattering," (Final Office Action, at page 6). This represents a fundamental misunderstanding of the invention, and a complete ignorance of large portions of the written description which relate to Appellants' invention. The portion of the specification cited by the Examiner appears in a section of the specification entitled "Optical Geometry, Other Apparatus, and Mode of Operation," and deals with the dimensional aspects of the invention (for example, sample depth, detector distance and detector area). The portion cited by the Examiner from pages 14 and 15 of the specification has nothing whatsoever to do with the particular wavelengths that are used to irradiate the unaltered whole blood sample. As explained above, the radiation wavelengths

selected in accordance with Appellants' invention include some that are selected to maximize absorbance and minimize scattering, and some that are selected to maximize scattering relative to absorbance.

Specifically, the Examiner's citation to lines 25-31 of page 15 is completely out of context and stops just short of the passage spanning page 15, line 33 to page 16, line 10, where it is explained:

> However, it should be noted that the optical geometry presented above, when used alone, does not attain commercially acceptable accuracy, i.e. it does not measure the relative hemoglobin concentrations to an accuracy of 1% or less. The optical apparatus of the present invention achieves commercially acceptable accuracy when used in combination with the corrections (described below) that correct the hemoglobin concentration measurements for the effects of light scattering by the red blood cells, for nonspecific light-scattering losses, and for the effects of the finite spectral bandwidth of the plurality of substantially monochromatic wavelengths.

That transition is followed immediately by sections 3, 4 and 5 of the specification (covering pages 16-38) that present detailed discussions of the selection of wavelengths for measuring, the use of additional wavelengths for scattering correction, and the correction for the effects of finite spectral bandwidth. The Examiner's rejection as applied to claims 1-36 is thus seen to be completely unfounded.

With respect to claims 37-44, the Examiner appears to be ignoring that both n and k are expressly required to be <u>integers</u> in claim 37, with n > k. Within the context of claim 37, particularly in light of the disclosure at page 20, lines 24-29 of the specification quoted above, "n - k" can only mean "n minus k". Those integer numbers and the difference between them are then used consistently throughout dependent claims 38-44.

With regard to claim 38, the Examiner questions how "coefficients of vectors [can] be equal to concentrations?" [Final Office Action, at page 8.] That concept is explained thoroughly in the specification as originally filed for example, the equation appearing at line 16 of page 21 and supporting text.

Turning finally to the various allegations of lacking antecedent basis appearing at the top of page 9 of the Final Office Action, claim 37 provides antecedent for the references to "wavelengths" appearing in claims 39 and 41. With respect to the other objection to claims 41 and 44, the cited passages are clear as they stand, and requiring Appellants to change "the" to "a" in each instance would seem to serve no useful purpose.

* * *

In light of the foregoing comments, Appellants respectfully request the reversal of the rejection of the claims under 35 U.S.C. § 112, second paragraph.

E. Conclusion and Relief Requested

Appellants believe the foregoing to respond fully to all of the rejections stated in the Final Rejection. The Board is respectfully requested to reverse all of the rejections stated in that Final Rejection, thus permitting the issuance of a timely Notice of Allowance for claims 1-44.

Respectfully submitted,

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APPENDIX

CLAIMS ON APPEAL

SN 07/953,680

1. A method of determining the concentrations of a plurality of constituent components of unaltered whole blood of unknown composition, including:

generating a plurality of substantially monochromatic radiation wavelengths, each wavelength of an absorbance subset of said plurality of wavelengths having been selected by their ability to distinguish the constituent components and having been selected to minimize the effects of radiation scattering and to maximize radiation absorbance by said constituent components, and each wavelength of a scattering subset of said plurality of wavelengths having been selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance by unaltered whole blood;

irradiating a sample of unaltered whole blood of unknown composition with said plurality of radiation wavelengths, through a depth of said sample chosen to minimize radiation scattering by unaltered whole blood;

detecting intensities of said radiation wavelengths, after passing through said depth of said sample, at a distance from said sample, and over a detecting area, both chosen to minimize the effects of radiation scattering by unaltered whole blood on the determination of concentrations of said constituent components; and

calculating concentrations of said plurality of constituent components of said sample of unaltered whole blood corrected for the effects of radiation scattering, based upon detected intensities of each of said plurality of radiation wavelengths, and based upon predetermined molar extinction coefficients for each of said constituent components at each of said plurality of radiation wavelengths.

2. The method of claim 1, wherein said depth of said sample is in the range of 80 to 150 micrometers.

3. The method of claim 2, wherein said depth of said sample is approximately 90 micrometers.

4. The method of claim 1, wherein said detecting area is at least approximately 150 square millimeters.

5. The method of claim 4, wherein said detecting area is at least approximately 600 square millimeters.

6. The method of claim 1, wherein said distance from said sample is within the range of 0 to 10 millimeters.

7. The method of claim 6, wherein said distance from said sample is approximately 1 millimeter.

8. The method of claim 1, wherein said step of detecting is performed over a half-aperture angle of radiation emanating from said sample of at least approximately 30 degrees.

9. The method of claim 8, wherein said step of detecting is performed over a half-aperture angle of radiation emanating from said sample of at least approximately 70 degrees.

10. The method of claim 1, further comprising:

correcting said calculated concentrations of constituent components for the effects of finite spectral bandwidth of the substantially monochromatic wavelengths on the extinction coefficients of each constituent component.

11. The method of claim 1, said plurality of constituent components including HbO_2, HbCO, Hi and Hb, said method further comprising:

before said generating step, selecting four radiation wavelengths by computing an error index for each of HbO_2, HbCO and Hi as the sum of the absolute values of the errors that are induced in the measurement of relative concentrations of $Hb0_2$, HbCO and Hi due to a change in optical density measurements; and

selecting a quadruple of radiation wavelengths having minimum error indices.

12. The method of claim 11, each one of said quadruple of radiation wavelengths being within the range of 510 to 630 nanometers.

13. The method of claim 12, said quadruple of radiation wavelengths comprising 522, 562, 584 and 600 nanometers.

14. The method of claim 12, said quadruple of radiation wavelengths comprising 518, 562, 580 and 590 nanometers.

15. The method of claim 12, said quadruple of radiation wavelengths comprising 520.1., 562.4, 585.2 and 597.5 nanometers.

16. The method of claim 12, said constituent components further including, bilirubin, said method further comprising:

before said generating step, selecting a radiation wavelength within the range of 475 to 500 nanometers as the radiation wavelength for the measurement of bilirubin.

17. The method of claim 16, said radiation wavelength for the measurement of bilirubin being 488.4 nanometers.

18. The method of claim 12, said constituent components further including sulfhemoglobin, said method further comprising:

before said generating step, selecting a radiation wavelength within the range of 615 to 625 nanometers as the radiation wavelength for the measurement of sulfhemoglobin.

19. The method of claim 18, said radiation wavelength for the measurement of sulfhemoglobin being 621.7 nanometers.

20. the method of claim 1, further comprising:

correcting said calculated concentrations of constituent components for the effects of light scattering by red blood cells.

21. The method of claim 20, said correcting step comprising, correcting said calculated concentrations of constituent components as a function of the relative concentrations of the constituent components.

22. The method of claim 21, said correcting step further comprising:

iteratively determining a red blood cell scattering vector for the particular composition of the whole blood sample being analyzed; and

using said red blood cell scattering vector to correct said calculated constituent component concentrations.

23. The method of claim 1, further comprising:

correcting said calculated constituent component concentrations for the effects of non-specific light scattering.

24. The method of claim 23, said correcting step comprising, correcting said calculated concentrations of constituent components as a function of the relative concentrations of the constituent components under consideration.

25. The method of claim 24, said correcting step further comprising:

iteratively determining a non-specific scattering vector for the particular composition of the whole blood sample being analyzed; and

using said non-specific scattering vector to correct said calculated constituent component concentrations.

26. The method of claim 1, further comprising, correcting said calculated concentrations of constituent components for the effects of light scattering by red blood cells and for the effects of non-specific light scattering.

27. The method of claim 26, said correcting step comprising, correcting said calculated concentrations of constituent components as a function of the relative concentrations of the constituent components under consideration.

28. The method of claim 27, said correcting step further comprising:

iteratively determining a red blood cell scattering vector for the particular composition of the whole blood sample being analyzed;

iteratively determining a non-specific scattering vector for the particular composition of the whole blood sample being analyzed; and

using said non-specific scattering vector and said red blood cell scattering vector to correct said calculated constituent component concentrations.

29. The method of claim 28, said plurality of constituent components including HbO_2, HbCO, Hi and Hb, said method further comprising:

before said generating step, selecting four radiation wavelengths by computing an error index for each of HbO_2, HbCO and Hi as the sum of the absolute values of the errors that are induced in the measurement of relative concentrations of HbO_2, HbCO and Hi due to a change in optical density measurements; and

selecting a quadruple of radiation wavelengths having minimum error indices.

30. The method of claim 29, each one of said quadruple of radiation wavelengths being within the range of 510 to 630 nanometers.

31. The method of claim 30, said constituent components further including bilirubin, said method further comprising:

before said generating step, selecting a radiation wavelength within the range of 475 to 500 nanometers as the radiation wavelength for the measurement of bilirubin.

32. The method of claim 31, said constituent components further including sulfhemoglobin, said method further comprising:

before said generating step, selecting a radiation wavelength within the range of 615 to 625 nanometers as the radiation wavelength for the measurement of sulfhemoglobin.

33. The method of claim 32, further comprising, before said generating step, selecting a radiation wavelength within the range of 635 to 645 nanometers as an additional radiation wavelength for the measurement of sulfhemoglobin.

34. The method of claim 20, said correcting step comprising,

correcting said calculated concentrations of constituent components as a function of wavelength.

35. The method of claim 23, said correcting step comprising,

correcting said calculated concentrations of constituent components as a function of wavelength.

36. The method of claim 26, said correcting step comprising,

correcting said calculated concentrations of constituent components as a function of wavelength.

37. A method of determining the concentrations of a plurality of k constituent components of unaltered whole blood, k being an integer, comprising:

generating a plurality of n different substantially monochromatic radiation wavelengths, where n is an integer and n > k, k of said n wavelengths having been selected to measure radiation absorption by said k constituent components, and n - k of said n wavelengths having been selected to compensate for errors due to n - k scattering factors in unaltered whole blood;

irradiating a sample of unaltered whole blood with said n radiation wavelengths;

detecting intensities of said n radiation wavelengths after passing through said sample of unaltered whole blood; and

calculating concentrations of said k constituent components of said sample of unaltered whole blood, corrected for the effects of radiation scattering, as a function of said detected intensities of said n radiation wavelengths.

38. The method of claim 37, said calculating step comprising:

calculating a vector of n optical densities of said sample of unaltered whole blood, each optical density being a function of a respective one of said n detected intensities; and

calculating said concentrations of said k constituent components using a set of n linear equations that equate said vector of n optical densities with a linear combination of k light absorbance vectors and n - k light scattering vectors, real coefficients of said

k absorbance vectors in said linear combination being equal to said concentrations of said k constituent components.

39. The method of claim 38, wherein each of said k light absorbance vectors corresponds to a specific one of said k constituent components, the entries of each light absorbance vector being extinction coefficients of a corresponding constituent component at each of said n wavelengths.

40. The method of claim 38, wherein each of said n - k light scattering vectors corresponds to an identifiable scattering factor, said method further comprising, iteratively determining each of said n - k scattering vectors as functions of said concentrations of said k constituent components present in said sample of unaltered whole blood.

41. The method of claim 37, said calculating step comprising, correcting said calculated concentrations of said k constituent components for the effects of finite spectral bandwidth of the n substantially monochromatic wavelengths on the extinction coefficients corresponding to each constituent component.

42. The method of claim 37, said generating step comprising:

selecting four radiation wavelengths by computing an error index for each of HbO_2, HbCO and Hi as the sum of the absolute values of the errors that are induced in the measurement of relative concentrations of HbO_2, HbCO and Hi due to a change in optical density measurements; and

selecting a quadruple of radiation wavelengths having minimum error indices.

43. The method of claim 37, said calculating step comprising, correcting said calculated concentrations of said k constituent components as a function of the relative concentrations of the k constituent components.

44. The method of claim 37, said calculating step comprising:

iteratively determining a red blood cell scattering vector for the particular composition of the unaltered whole blood sample being analyzed;

iteratively determining a non-specific scattering vector for the particular composition of the unaltered whole blood sample being analyzed; and

using said red blood cell scattering vector and said non-specific scattering vector to correct said calculated concentrations of said k constituent components.